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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Papisov *et al.* Examiner: Yong Liang Chu
Serial No: 10/521,334 Group Art Unit: 1626
Filing Date: October 27, 2005 Confirmation No.: 1459
Title: OXIME CONJUGATES AND METHODS FOR THEIR FORMATION AND USE

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Claims in the present case stand rejected under 35 U.S.C. § 103(a) as unpatentable over Cervigni *et al.*, in view of U.S. Patent No. 5,958,398 by Papisov (“the ‘398 patent”), U.S. Patent No. 5,612,037 by Huebner (“the ‘037 patent”), and G. Hermanson, Preparation of Liposome Conjugates and Derivatives, Bioconjugate Techniques, pp. 552-589, (“Hermanson”). The rejections are clearly improper. Applicant submits herewith Notice of Appeal and fee of \$270.00 pursuant to 37 C.F.R. § 41.20(b)(1) has been provided by the USPTO’s Electronic Filing System’s credit card payment option. Accordingly, Applicant respectfully submits that the present Request is timely filed on July 29, 2010.

Levied 103(a) Rejection is Improper

The Examiner has rejected claims 1-6, 11, 12, 14, 19, 20, 41-43, and 63-71 over Cervigni in view of the ‘398 patent (see pages 2-4 of the Office Action mailed April 30, 2010 and pages 2-3 of the Office Action mailed July 15, 2009). It is unclear if the current rejection is still further in view of the ‘037 patent and Hermanson. The rejection is clearly improper for at least the following reasons:

- i) The Examiner has impermissibly used the content of the specification as basis for the obviousness rejection.
- ii) The Examiner has dismissed a demonstrated state of the art in his arguments maintaining the obviousness rejection.

In the Office Action dated October 24, 2008, the Examiner stated that “a conjugate of polyacet[al] or polyketals with a modifier through an oxime-containing li[n]ker are taught, suggested and motivated from the combined references” and “in terms of the argument of a reasonable expectation of success [...] a reasonable stability of polyacet[al] or polyketals from nucleophilic attack is predictable to one ordinary skilled in the art by choosing appropriate reaction conditions without undue experimentation.”

In response, Applicant explained the state of the art at the time the present application was filed, including by providing an additional publication (Papisov, *ACS Symposium Series* 786:301, 2001), and demonstrated that, a person of ordinary skill in the art, reading Cervigni and the ‘398 patent, would (1) not be motivated to perform the conjugation described by Cervigni on the polyacetals of the ‘398 patent (due, for example, to known instability problems of polyacetals described in the ‘398 patent under acidic conditions), and (2) would not have a reasonable expectation of success of preparing the claimed conjugates even if so motivated (see pages 3-4, 3rd-4th paragraphs of Response filed April 24, 2009). Indeed, Applicant pointed out that those of ordinary skill in the art, reading Cervigni and the ‘398 patent in the context of the art at the time, would have appreciated that use of the Cervigni conditions with the ‘398 patent compounds would not generate the claimed conjugates, but rather would result in nearly complete hydrolysis of the PHF main chain (see page 3, 1st full paragraph, of Response filed April 24, 2009).

In the Office Action dated July 15, 2009, the Examiner maintained the rejection, asserting that Cervigni teaches alternative, more mild conditions (by way of a citation to yet another reference, Rose) for oxime formation.

In the Response filed January 15, 2010, Applicant explained that the conditions in fact described by Cervigni were not actually “mild” with respect to PHF. Moreover, Applicant provided *evidence*, in the form of a Declaration under 37 CFR § 1.132, executed by an inventor of the present invention further explaining the state of the art at the time the present application, and explaining how one of ordinary skill of the art *who did not have the benefit of the present specification* would have understood the teachings of Cervigni and the ‘398 patent. As set forth in detail in the Declaration, at the time the instant application was filed, the state of the art—at best—indicated a significant level of unpredictability regarding the reactivity and stability of polyacetals. Applicant explained why, in light of the state of the art, it would not have been obvious to one of ordinary skill in the art to combine the Cervigni (or Rose) oxime-forming conditions with the polyacetals of the ‘398 patent (see page 12, 1st sentence of Response filed January 15, 2010).

In the current Office Action mailed April 30, 2010, the Examiner refers to Applicant's Declaration under 37 CFR § 1.132 and states:

"The key argument Applicants made here is that an oxime-containing polyketal and polyacetal **is not** stable under acidic conditions (i.e. at pH ~4) due to the stability of polyacetals or poly[ketals]. However, at lines 1-4, paragraph [0279], page 92 of the instant specification, it states that the coupling reaction between PHF diol and the couple reagent VII was carried out at pH = 3.0 by addition of 1M NaHSO₄ and agitated for 2 hours on the ice. This disclosure clear[ly] contradicts with the statement Applicants made in the instant 132 Declarations, namely an oxime-containing polyketals and polyacet[al] conjugate **is not** stable under acidic conditions" (emphasis added).

Thus, the Examiner maintains the rejection by dismissing the Declaration on the ground that *the present specification* provides information, not found in the prior art, that shows the prior art understanding/expectation in fact was incorrect and it is possible to produce the claimed invention. The Examiner thus *relies on the present invention* to reject the present claims! This reliance is impermissible. Applicant has *demonstrated*, through submission both of published literature and of sworn declaration testimony, that those of ordinary skill in the art, reading the cited references in the absence of the present disclosure, would *not have been motivated to try* to use the Cervigni methods to generate conjugates of the '398 compounds and, moreover, even if for some reason they were so motivated to try, would not have had a reasonable expectation of success.

The alleged contradiction between Applicant's Declaration under 37 CFR § 1.132 and the present specification is incorrect. The Declaration speaks to the state of the art prior to the filing of the present application, and does not indicate the claimed conjugates are not stable under acidic conditions; rather, it indicates what would have been known to the skilled artisan at the time the present application was filed. In fact, Applicant submits that regarding the stability of polyacetals, any difference between the state of the art at the time the present application was filed and Applicant's disclosure represents evidence of unexpected results, not contradictory statements as asserted by the Examiner.

The *present disclosure* provides the teaching, unexpected in light of the state of the art, that claimed conjugates *can* be made under acidic conditions. The Examiner may not rely on the *present specification* for motivation to combine cited references to render obvious the present claims, and in

doing so the Examiner has impermissibly used the content of the specification as basis for the obviousness rejection.

Furthermore, the Examiner's apparent dismissal of Applicant's Declaration on the grounds that it does not contain comparative data is unreasonable if not illogical, particularly in the instant case where the utility of comparative data isn't even clear. The purpose of the provided Declaration was to describe the state of the art prior to Applicant's disclosure, not compare prior conjugates with Applicant's conjugates.

For all of these reasons, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is improper and therefore the Examiner has not established a *prima facie* case of obviousness with respect to claims 1-6, 11, 12, 14, 19, 20, 41-43, and 63-71. Applicant respectfully requests that the rejection be removed.

Levied Obviousness-type Double Patenting Rejection is Improper

In the Office Actions dated February 4, 2008, and October 24, 2008, a provisional obviousness-type double patenting rejection was levied against claims 1-12, 14, 19-22, and 41-43 for being unpatentable over claims 29-42 of copending Application No. 10/501,565 (the '565 application) in view of Cervigni, the '037 patent, and Hermanson. In the responses filed August 4, 2008, and April 24, 2009, Applicant requested that this provisional rejection be held in abeyance to be addressed when a relevant claim of the '565 application issues. While not mentioned in the two most recent Office Actions, it appears this rejection is still of record and Applicant believes the rejection is improper for at least the following reason:

- i) The Examiner did not establish a *prima facie* case of obviousness regarding the combination of claims 29-42 of the '565 application with the other references in the Office Action dated February 4, 2008.

In the rejection, the Examiner states that "the '565 application claims a biodegradable biocompatible polyketal polymer [...] with a nitrogen-containing moiety" and that using a "polyketal as a carrier of the conjugate in claims 12 and 14 has been claimed in the '565 application as a biodegradable polyacet[al] polymer [...] and suggested to crosslink with a drug to form a conjugate." Applicant respectfully traverses and points out that the word "crosslink" does not appear in claims 29-42 of the '565

application, although it does appear in claim 27 of the ‘565 application. Even so, the Examiner has not established why (or how), in view of Cervigni, one of ordinary skill in the art would be motivated to select “pharmaceutically useful group” and “nitrogen-containing moiety” from separate claims in the ‘565 application, combine them into a single moiety appended and/or crosslinked to the polyketals of the ‘565 application, and arrive at Applicant’s claimed conjugates having an oxime-containing crosslinker.

Applicant respectfully submits that the double patenting rejection is improper and therefore the Examiner has not established a *prima facie* case of obviousness with respect to claims 1-12, 14, 19-22, and 41-43. Applicant respectfully requests that the rejection be removed. Applicant reserves the right to obviate this rejection by filing a terminal disclaimer.

Applicant invites the Examiner to call the undersigned at (617) 248-5175 with any questions pertaining to the above-identified application in order to expedite prosecution of this case.

Respectfully submitted,

Dated: July 29, 2010

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